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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/632,815	08/04/2003	Martin Opper	38005-0183	4607

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 06/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/632,815	OPPER ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 17-23 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 17-23 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 8/4/2003.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-16 have been canceled. Claims17-19 have been amended. Claims 17-23 are pending and under consideration.

Specification

The specification is objected to for lacking of Sequence Compliance for Figures 1a, 2a and 5b-5i as well as page 14, lines 8-10 and 18-20.

Claim Objections

Claims 17-22 are objected to for failing to comply with the Sequence Rules. Amendment of the claims to reflect the Sequence Identifiers used to amendment the Specification in order to overcome the objection above, will overcome this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claim contains two periods. following the first period is a hypothetical name in italics. It is unclear whether this portion is part of the claim. For purpose of examination, the claimed vector will be considered as comprising the polynucleotides encoding the italicized fusion protein.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-23 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

(a)Claim 23 is drawn to the vector pTrc99 dicistr Fab-E.coli-B-Gluc. The claim fails to specify a single nucleic acid sequence for this vector encoding Fab-E.coli-B-Gluc, or the single nucleic acid sequence of the "empty" vector. The specification provides some mapping of restriction sites on the vector (Figure 4), but this does not provide a complete characterization of said vector. Amendment of the claim to dependency on a deposited cell line comprising said vector, or amendment of the claim to a SEQ ID NO would overcome this rejection.

(b)Claims 17-19 are drawn to nucleic acid sequences encoding a fusion protein comprising any antibody or any antibody fragment with the enzyme E coli B-glucoronidase. The specification describes the nucleic acids encoding E coli B-glucoronidase and nucleic acid encoding the Mab 431/26. the specification fails to describe any other nucleic acids comprising other antibodies or portions of antibodies. The findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated,

does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. In the instant case the claims drawn to nucleotide sequences encoding a fusion protein require the nucleotide sequences of the genus of antibodies and antibody fragments encompassed by the claims. The art recognizes that in order to produce recombinant antibodies or antibody fragments that bind to antigens, the nucleic acid sequences of the variable chains or complimentary determining region, are necessary (Jones et al., Advanced Drug Delivery Reviews 1998, page 154, column 1, lines18-26, and page 160, lines 24-25). The description of a nucleic acid sequence encoding Mab 431/26 clearly fails to describe the genus of nucleic acid sequences encoding antibodies or antigen-binding fragments of antibodies because the variable chains of antibodies are highly variant in order to accommodate binding to different antigens. One of skill in the art would reasonable conclude that applicant was not in possession of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al (Cancer Research, 1992, Vol. 52, pp. 4484-4491) in view of Bosslet et al (Cancer Research, 1994, Vol. 54, pp. 2151-2159) and Friend et al (WO 93/22334).

Claim 17 is drawn to a nucleotide sequence encoding a fusion protein comprising an antibody or an antibody .

Wang et al teach a fusion protein comprising an antibody which binds to an antigen expressed on the surface of hepatoma cells fused to E coli beta-glucoronidase (lines 12-14 of abstract and page 4484, second column, lines 18-21 and lines 29-32 and lines 5-6 under the heading "Materials and Methods").. Wang et al does not teach a fusion protein or the nucleic acid encoding said fusion protein.

Bosslet et al teach a fusion protein of an antibody which binds to CEA fused to human Beta glucoronidase (page 2151, first paragraph of "Purification and Analysis of Fusion Protein"). Bosslet et al teach that the administration of the fusion protein does not require a second step to clear the antibody-enzyme conjugate from the plasma before pro-drug administration because the parenchymal cells of the liver will internalize the remainder of the non-bound fusion protein by means of the mannose-6-phospshate and galactose-receptor mediated uptake (page 2157, first column, lines 16-34).

Friend et al teach that bacterial glucoronidase has an optimum turnover at ph 6.5 whereas mammalian glucoronidase has an optimum turnover at pH 4 (page 15, lines 5-8).

It would have been prima a facie obvious at the time the invention was made to construct a fusion protein comprising nucleic acids encoding the antibody of Wang et al and the E coli beta- glucoronidase of Wang et al. One of skill in the art would have been motivated to do so by the teachings of Bosslet et on the alternate use of fusion protein rather than conjugates. One of skill in the art would understand that the nucleic acid encoding a fusion protein would be a more stable and reliable source of protein comprising both the enzyme and the antibody because it would not be subject to chemical manipulations in the production of a conjugate which can vary from batch to batch. One of skill in the art would also have been motivated to retain the E coli beta glucoronidase of Wang et al rather than using the human glucoronidase of Bosselt et al because of the teachings of Friend et al on the higher turnover rate afforded by the bacterial enzyme at pH 6.5 versus the human enzyme. One of skill in the art would have been motivated

to use a nucleic acid encoding the bacterial version of beta glucoronidase so as to have more enzymatic activity available to release active drug at the tumor site. It would have been further obvious to one of skill in the art that excess fusion protein comprising the E coli B glucoronidase would also be taken up by the liver parenchymal cells and thus would be broken down in the lysosomal compartment rather than being present in excess amounts in the circulation and potentially contributing to an immunogenic reaction against the E coli enzyme.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.
6/26/2005